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Malignant Peripheral Neuroectodermal Tumor in an Infant With Neurofibromatosis Type 1

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A case of multifocal malignant peripheral neuroectodermal tumor (PNET) arising from a plexiform neurofibroma in a 4-month-old Chinese boy with neurofibromatosis type 1 (NF-1) is described. Cytogenetic culture demonstrated hypotriploid karyotype with an abnormal clone characterized by 59–60, XY, +2, +3, +6, +8, +8, +12, +i(13)(q10), +der(14)t(1;14)(q21;q32), +16, +19, +20, +mar[cp3] with no apparent abnormality of chromosome 17. The child was treated with combination chemotherapy comprising ifosphamide, vincristine and doxorubicin. Despite initial partial response the child finally died of tumor progression and pulmonary metastases 8 months after diagnosis. We believe this is the first reported case of PNET in a child with NF-1 and may support an association between these two disorders of neural crest origin.

Key words: primitive neuroectodermal tumor, neurofibromatosis, neural crest

INTRODUCTION

Peripheral primitive neuroectodermal tumor (PNET) is a group of soft tissue tumors of presumed neural crest origin that arise outside the brain, spinal cord, and sympathetic nervous system [1]. It tends to present in older children, is highly aggressive with a high local recurrence rate and responds poorly to therapy. Neurofibromatosis, a common neurocutaneous syndrome, is also a disorder of neural crest origin. Neurofibrosarcoma, neuroblastoma and pheochromocytoma were all found to be more common in neurofibromatosis [2]. We report a case of PNET in an infant with neurofibromatosis. Such an early onset and association has not been described previously in the literature.

CASE REPORT

A male infant of Chinese origin was born with a diffuse, pigmented and nodular mass involving his entire anterior abdominal wall, lower back, buttock and upper part of the thighs including the scrotum, compatible with the findings of a plexiform neurofibroma. In addition, a large cafe au lait spot measuring 3 cm in diameter over his right leg and two smaller spots over his left thigh and right upper arm were also found, suggestive of neurofibromatosis type 1 (NF-1). Both parents were free of the stigmata of NF-1 but a paternal uncle died of leukemia at the age of 24 years.

At 1 month of age a growth of 1 cm diameter was detected over the neuroma at his lower back. An excision biopsy was interpreted as a melanocytic lesion. One month later, the mass recurred at the same site with another growth over his left flank and right groin, all of which being over the plexiform neurofibroma. The mass at the original site was reexcised and histologically reported as "schwannoma." Because of the diagnostic uncertainty, the child was referred to our unit at the age of 4 months.

Initial physical examination showed an active and alert child with normal growth parameters. Apart from the stigmata of NF-1 described, a fleshy mass was noted over his left flank measuring 1.5 cm in diameter. The mass at the right groin had grown to 5 × 3 cm in maximum dimensions (Fig. 1). In addition the right scrotum was filled with tumor tissue and the testicle was indistinct. Plain x-rays of the chest, abdomen, and the long bones were normal. Computed axial tomography scan of the thorax and abdomen revealed extensive cutaneous and subcutaneous soft tissues involving the lower part of the

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Fig. 1. A male infant with neurofibromatosis type 1 showing an extensive plexiform neuroma with a big fleshy mass over his right iliac region.

trunk and the scrotum. The internal organs appeared normal. The urinary catecholamine was normal and the bone marrow aspiration and biopsy was clear of malignant cells. The diagnosis of peripheral PNET was made according to the histopathological and immunohistochemical features.

Both surgery and radiotherapy were considered inappropriate because of the extensive underlying plexiform neuroma which involved over 50% of the skin. In fact, one of the biopsy sites developed prolonged oozing and poor healing. Chemotherapy comprised doxorubicin 15 mg/m^2 daily for 3 days, ifosphamide 2,200 mg/m^2 daily for 3 days, and vincristine 1.5 mg/m^2 at 3 to 4 weekly cycles. This was complicated by prolonged neutropenia and sepsis after each course and he required granulocyte colony stimulating factor rescue once. Despite an initial reduction in size, the tumor soon became resistant and two pulmonary metastases appeared after the fifth course of chemotherapy. Active treatment was stopped and the child was supported symptomatically. He finally died at 12 months of age.

PATHOLOGY

Excised ellipses of skin and tumor tissue measuring approximately 5 × 5 × 2 cm were examined. Under low power there was cellular tumor tissue present which extended from the dermis to the subcutis. At the dermal interface this tumor proliferation gave a lobular architecture to the skin surface with invaginations of the squamous epithelium seen (Fig. 2). Prominent junctional activity of naevus cells was seen with reactive atypia but a diagnosis of melanoma could not be ascertained. The tumor had a histological picture present which varied from field to field. In some areas there were features characteristic of a diffuse and plexiform neurofibroma. In other areas the tumor cells were small with a high nucleocytoplasmic ratio and with microcystic spaces, compatible with a primitive neuroectodermal tumor (Fig. 3). A transition between the primitive and mature areas was seen. Immunohistochemical staining for neuron-specific enolase was negative but S100 positivity was present. No immunohistochemical evidence of rhabdomyosarcoma and no PAS positivity was seen in the tumor cells.

A cell suspension of the tumor was made and cultured for preparation of metaphases for cytogenetic studies essentially as described [3]. G-banding was performed and 3 metaphases were analysed. The karyotype [4] of the tumor revealed hypotriploidy and structural abnormalities of chromosomes 14 and 13 and an unidentified marker, i.e., 50–60, XY, +2,+3,+6,+8+8,+12,+i(13)(q10),+der(14)t(1;14)(q21;q32),+16,+19,+20,+mar[cp3]. There was no apparent abnormality with chromosome 17. The metaphase is shown in Figure 4a and is representative of the other metaphases analysed.

DISCUSSION

PNET was originally described by Stout [5] as a tumor arising in peripheral nerve and containing rosettes. This is a group of neoplasms which arise from pluripotential neural crest cells and present predominantly in the pediatric age group. It excludes those originating from the central nervous system, adrenal gland and sympathetic ganglia [1]. It has been described in the chest wall as Askin tumor [6], bone [7], and testis [8].

PNET is an uncommon form of malignancy and has to be differentiated from other small round cell tumors of children. Negative staining with markers for striated muscles, leukocytes, and even some of the neural tissues helps to distinguish PNET from most other tumors. Positive cytochemical reactions for neuron-specific enolase [9], neurofibrillar protein, S100 protein [10] and a nonrandom chromosomal reciprocal translocation (11;22)(q24;q12) give further support for the diagnosis of PNET [11]. Considerable overlap exists between PNET and extraosseous Ewing's sarcoma. Marina et al. [1] and

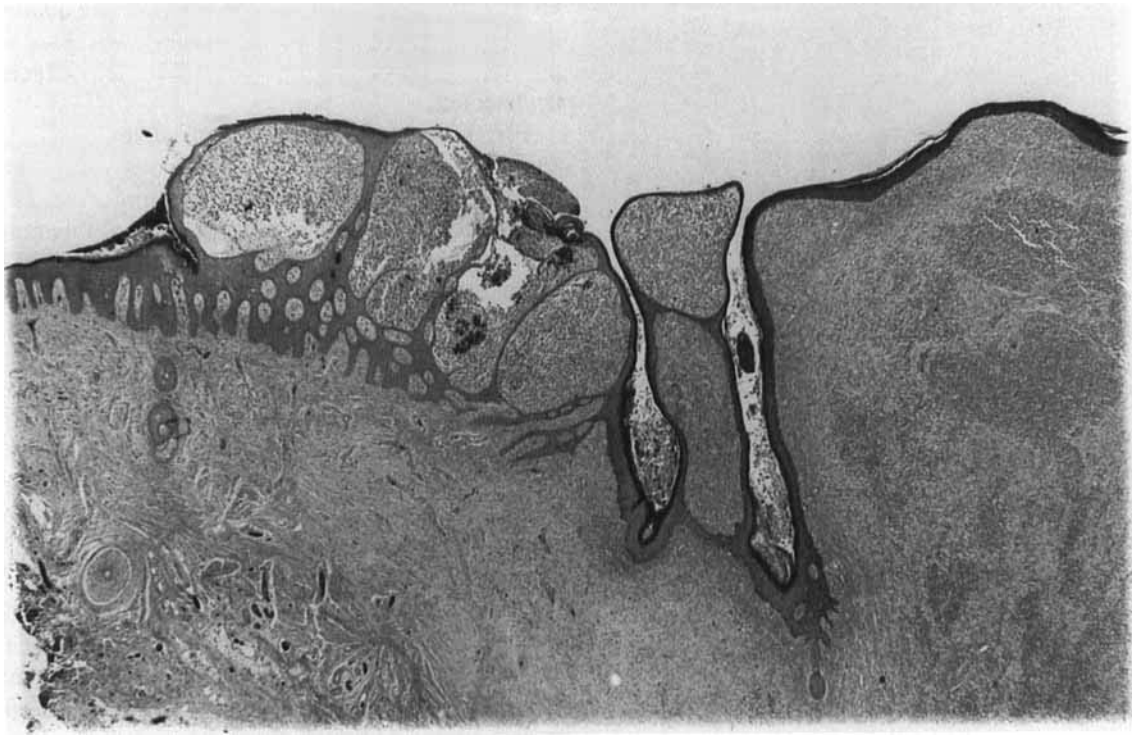

Fig. 2. Excised tumor tissue under low power showed cellular tumor tissue present which extended from the dermis to the subcutis. At the dermal interface this tumor proliferation gave a lobular architecture to the skin surface with invaginations of the squamous epithelium.

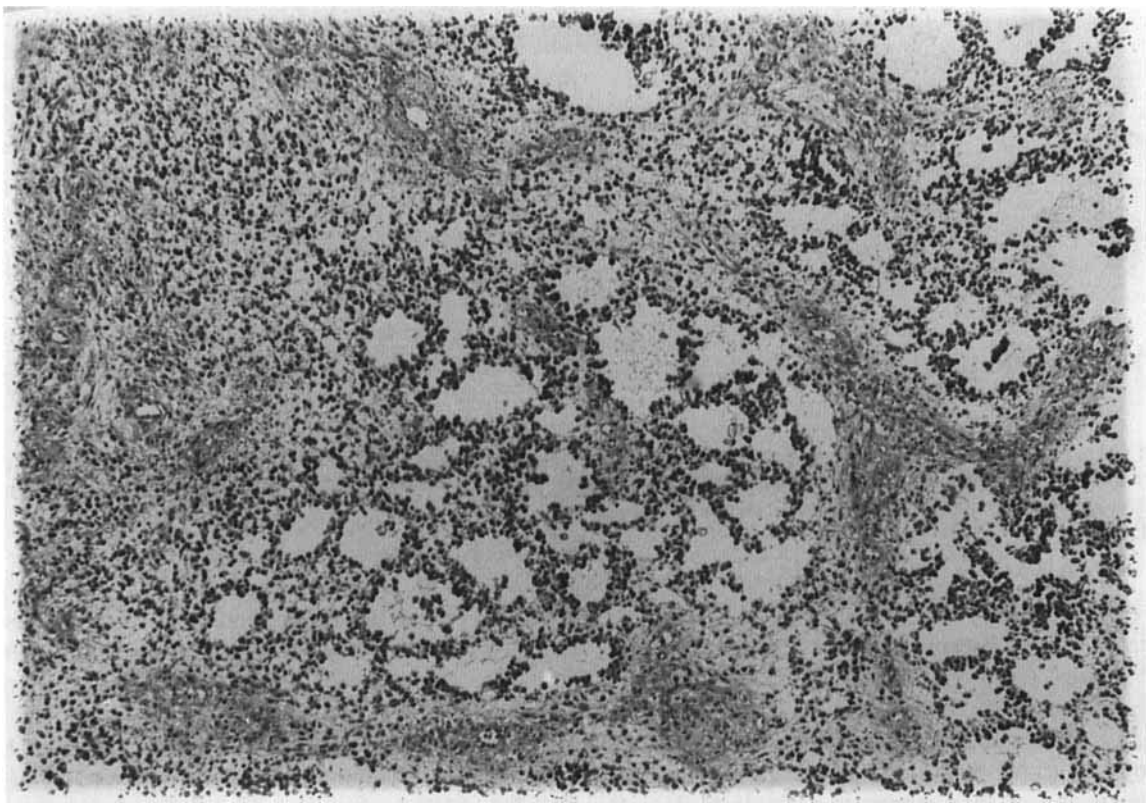

Fig. 3. Under high power the tumor cells were small with a high nucleocytoplasmic ratio and with microcystic spaces, compatible with a small round cell tumor and subsequent immunohistochemical staining, favored the diagnosis of primitive neuroectodermal tumor.

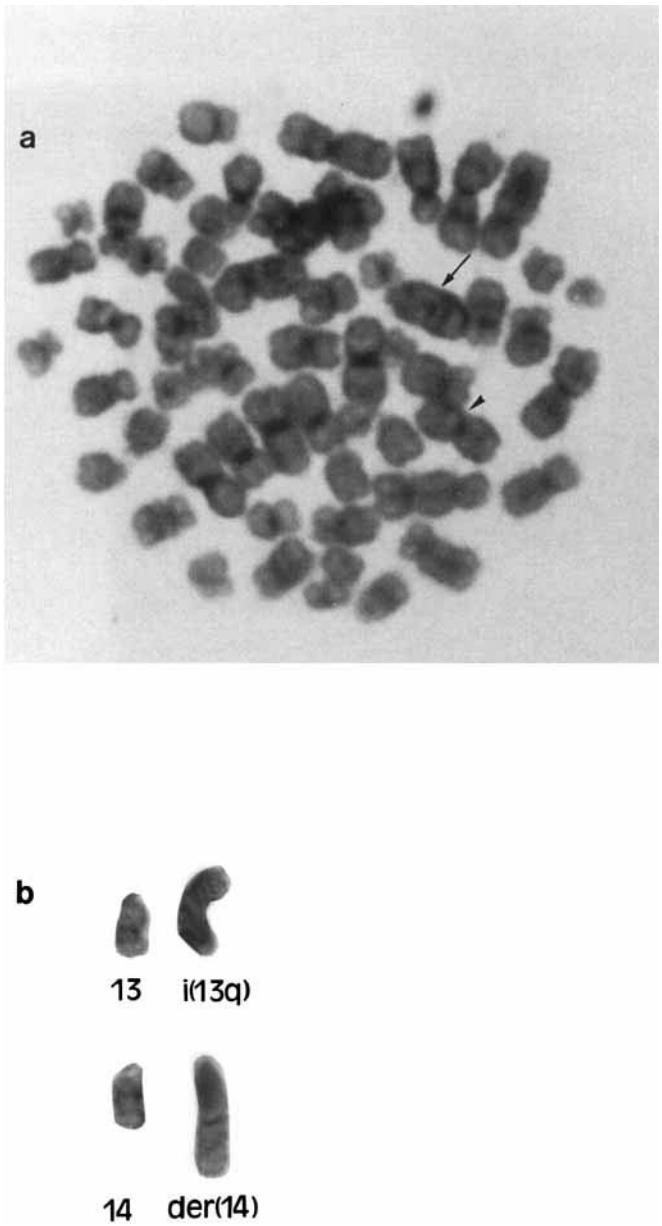

Fig. 4. **a:** G-banded metaphase from patient. Arrowhead indicates i(13)(q10) and arrow shows der (14). **b:** Partial karyotype of patient revealing structural abnormalities: (i) i(13)(q10) and (ii) der(14) t(1;14)(q21;q32).

Schmidt et al. [12] proposed different sets of criteria to differentiate the two. However, there is experimental evidence to suggest that PNET and Ewing's sarcoma may have the same neuronal histogenesis [13]. The observation that both tumors share the same chromosomal translocation t(11;22)(q24;q12) [11] gives further support that these two neoplasms may represent a single biological entity displaying various degrees of neuroectodermal differentiation. In our case, a hypotriploid karyotype with an abnormal clone was documented and the quality of the metaphases was such that definitive analysis was not possible and the presence of t(11;22)(q24;q12) could not be detected.

PNET occurs in children and adolescents at a mean age of 15.2 years [12]. No infant was reported to have this tumor. The most frequent location of PNET was in the thoracopulmonary region but 36% of this tumor was found in the pelvis and lower extremity. PNET is an aggressive tumor and has a median time of 10.8 months for dissemination [12]. Our patient was a male infant with the tumor mainly confined to the skin over the thoracoabdominal region. The tumor responded poorly to chemotherapy and he developed lung metastases 8 months after the initial presentation. Histologically, the tumor had no Homer-Wright rosettes and was negative for neuron-specific enolase, but evidence of neural differentiation and expression of S100 protein makes the diagnosis of PNET more likely than Ewing's sarcoma.

Our patient also had type 1 neurofibromatosis (NF-1). He fulfilled the diagnostic criteria of the National Institutes of Health Consensus Development Conference [14] by having a diffuse plexiform neurofibroma and the cafe au lait spots. Although there were only 3 cafe au lait spots, the huge plexiform neurofibroma which occupied more than 50% of his total body surface area could explain why not more of these macules were found. Although both parents had no stigmata of neurofibromatosis, his paternal uncle who died from leukemia may also have NF-1 since NF-1 can predispose to malignant myeloid disorders [15]. Our patient may therefore carry a new mutation for NF-1 or the NF-1 may be familial. The genetic locus of NF-1 has been mapped to 17q with its gene cloned and protein defined recently [16]. There was no apparent abnormality on chromosome 17 in the tumor karyotype of our case, but subtle abnormalities of chromosome 17 would not be detected easily.

NF-1 is a common neurocutaneous syndrome with a much higher frequency of brain tumor (43% compared to 1.7% in normal population) and neurofibrosarcoma (14% compared to 0.04%) [2]. The incidence of neuroblastoma and pheochromocytoma is also higher than expected [2]. Since these are tissues derived from neural crest, it strengthens the belief that neurofibromatosis is basically a neurocristopathy. A supratentorial primitive neuroectodermal tumor has been reported [17], but peripheral PNET has never been described in any patient with NF-1 except the present case. This may be due to the difficulty in differentiating PNET from the other small round cell tumor such as undifferentiated rhabdomyosarcoma which are more commonly found in neurofibromatosis [18]. In conclusion, our report presents an association between PNET and NF-1 which may be coincidental or represents genuine predisposition of patients with NF-1 to develop all kinds of neural crest tumor, including PNET.

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